REMARKS

Claims 56-81 are currently pending and under examination. The Applicants thank the Examiner for entering Claims 56-81. Claims 56-81 currently stand rejected. Applicants request that the following remarks be considered and that Claims 56-81 be found allowable in light of these remarks.

A Substitute Sequence Listing under 37 C.F.R. §1.825 is submitted herewith. The Substitute Sequence Listing is supported by the original disclosure and does not add new matter. Applicants request consideration of the following remarks concerning the Substitute Sequence Listing, and request that the Substitute Sequence Listing be entered.

Amendments to the specification are submitted herewith. Amendments to the specification are supported by the original disclosure and do not add new matter. Applicants request consideration of the following remarks concerning amendments to the specification, and request that these amendments be entered.

Regarding Objections to the Specification

Regarding the Substitute Sequence Listing

A Substitute Sequence Listing under 37 C.F.R. §1.825 is submitted herewith. The amended Substitute Sequence Listing, wherein SEQ ID NO: 1 discloses the amino acid sequence of the human myelin basic protein (MBP), does not contain new matter. The added material is supported by the original disclosure as filed on page 10 at lines 20-21 of the original specification of the present application as filed, which discloses "the human myelin basic protein, as shown in SEQ ID NO: 1." The added material is of record in the parent and grandparent applications to the present application (Ser. No. 09/007,520, now Pat. No. 6,258,781, and Ser. No. 08/327,357, now Pat. No. 5,817,629, respectively), wherein SEQ ID NO: 1 of the sequence listing in each patent is the 170 amino acid sequence of the human myelin basic protein (MBP), identical to the SEQ ID NO: 1 of the Substitute Sequence Listing.

The Substitute Sequence Listing identifies SEQ ID NO: 1 as a peptide from a clone of human myelin basic protein, and discloses the amino acid sequence of human myelin basic

protein as SEQ ID NO: 1. The 170 amino acid sequence of human myelin basic protein disclosed in SEQ ID NO: 1 of the Substitute Sequence Listing in the present application is identical to sequence of human myelin basic protein disclosed in SEQ ID NO: 1 in the parent and grandparent applications, now Pat. Nos. 6,258,781 and 5,817,629, respectively.

It should be noted that the original specification on page 10 at lines 20-21 of the present application, teaches a valine residue at amino acid position 87 (Val 87) and an isoleucine residue at amino acid position 93 (Ile93) "in the human myelin basic protein as shown in SEQ ID NO: 1." (Page 10 at lines 20-21). Such teaching provides further support for statement that SEQ ID NO: 1 in the Substitute Sequence Listing does not add new matter. In the previously submitted Sequence Listing, submitted on October 3, 2001, SEQ ID NO: 1 is identified as a "Synthetic Peptide" having forty-six (46) amino acids, and does not have a valine residue at amino acid position 87 (Val87) and an isoleucine residue at amino acid position 93 (Ile93) as taught in the specification on page 10 at lines 20-21. In the Substitute Sequence Listing, SEQ ID NO:1 is identified as human myelin basic protein having 170 amino acids, including a valine residue at amino acid position 87 (Val87) and an isoleucine residue at amino acid position 93 (Ile93) as taught in the specification on page 10 at lines 20-21. In the Substitute Sequence Listing, amino acids 61-106 of SEQ ID NO: 1 correspond to the amino acid sequence identified as 61 to 106 on page 12 of the original specification.

Support for the Substitute Sequence Listing submitted herewith is found in the specification and Sequence Listing of both the parent and the grandparent of the present application. In the parent application, Ser. No. 09/007,520 (the '520 application), now Pat. No. 6,258,781 (the '781 patent), a claim was made under 37 C.F.R. § 1.821(e) that the Sequence Listing and the computer readable form of the Sequence Listing were identical to the Sequence Listing submitted in its parent application, namely Ser No. 08/327,357, now Patent No. 5,817,629 (the '629 patent), which is the grandparent of the present application. (See, Application Serial No. 09/007,520, Letter Pursuant to 37 C.F.R. § 1.821(e), filed October 12, 1999). Inspection of the Sequence Listing in the grandparent '629 patent and the parent '781 patent shows that SEQ ID NO: 1 lists a 170-amino-acid sequence identified as a peptide from a clone of human myelin basic protein. SEQ ID NO: 1 of the '629 and '781 patents have a valine residue at amino acid position 87 (Val87) and an isoleucine residue at amino acid position 93

(Ile93) as taught in the specification of the '629 patent at column 6 at lines 22-23, in the '781 patent at column 6 at line 20-21, and in the present application at page 10, lines 20-21 of the specification as filed. In the Sequence Listing of the '629 patent and the '781 patent, amino acids 61-106 of SEQ ID NO: 1 correspond to the amino acid sequence identified in the specification as "Amino acids 61-106 of SEQ ID NO: 1" in the '629 patent at column 7 below line 31 and in the '781 patent at column 7 below line 29.

Thus, because the amended Substitute Sequence Listing submitted herewith contains the SEQ ID NO: 1 as found in the parent and grandparent applications to the present application, and as identified in the specifications of the parent, grandparent, and the present application, the amended Substitute Sequence Listing does not contain new matter and should be accepted. Applicants point out that SEQ ID NO: 2 through SEQ ID NO: 12 of the Substitute Sequence Listing is identical to the original Sequence Listing filed on October 3, 2001, in the present application.

Regarding amendments to the specification

The specification has been amended. The amendments to the specification contains no new matter. Applicants request consideration of the following remarks concerning amendments to the specification, and request that the replacement paragraphs submitted herewith, marked up to show changes relative to the immediate prior version, be entered into the record.

Support for these amendments is found on page 10 at lines 20-21 of the original disclosure as filed, and in the parent and grandparent application to the present application.

The specification has been amended to identify the amino acids of SEQ ID NO: 1 that correspond to the MBP peptides disclosed in the specification. The paragraph on page 5, line 24 to page 6 line 14, has been amended to identify the MBP peptides disclosed therein, by identifying the corresponding amino acids in SEQ ID NO: 1 of the Substitute Sequence Listing. Similarly, amendments were made to the specification on pages 10, 12,13, and 14 to identify the MBP peptides disclosed therein, by identifying the corresponding amino acids in SEQ ID NO: 1 of the Substitute Sequence Listing.

Support for amendments to the specification is found in the records of the parent and grandparent of the present application. The present application was filed as a continuation of

Application Serial No. 09/007,520 (the '520 application) now Pat. No. 6,258,781 (the '781 patent). The specification filed in the present application is identical to the specification filed in the '520 application. Thus, the original specification in the parent '520 application also recites "Val 87 and Ile 93 in the human myelin basic protein as shown in SEQ ID NO: 1" (page 10 at lines 20-21); the corresponding text in the '781 patent is found in column 6 at lines 20 to 21. The '520 application was filed with a preliminary amendment to enter amendments to the original specification of the '520 application. These amendments to the specification of the parent '520 application, entered by preliminary amendment, are the same as the amendments submitted herewith in the present application. In particular, the original specification of the '520 application was amended to correctly identify the amino acid sequence on page 12 of the original specification as "Amino Acids 61-106 of SEQ ID NO: 1" (added material underlined), and to identify other peptides in the specification as sequences corresponding to defined positions in human myelin basic protein (MPB) disclosed in SEQ ID NO: 1. The specification of '781 patent reflects the amendments made to the original specification of the '520 application by preliminary amendent. Because the amendments to the specification presented herein are of record in the parent '520 application, the present amendments to the specification do not introduce new matter.

Regarding rejections of claims

Claims 56-81 are currently pending in the application. Claims 56-81 stand rejected. Applicants request consideration of the following remarks concerning these rejections.

Double patenting rejections

Claims 56-81 stand rejected for obviousness-type double patenting as being allegedly upatentable over claims 1-9 of Patent No. 5,817,629. Applicants respectfully request that the obviousness-type double patenting rejections be held in abeyance until allowable subject matter has been indicated, at which time a terminal disclaimer will be filed. The filing of the terminal disclaimer is in order to further prosecution of the subject application and is not to be construed as acquiescing to the propriety of the rejection.

Rejections under 35 U.S.C. §112, first paragraph for lack of written description

Claims 56-81 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, it is alleged that Claims 56-81 are directed to additions, deletions and substitutions of a peptide having the sequence contained in the sequence of SEQ ID NO: 1. Applicants traverse this rejection.

The §112, first paragraph, written description requirement to show that the applicant was in possession of a claimed invention at the time of filing, can be satisfied by a sufficient description of a representative number of species by various disclosures, including disclosure of relevant identifying characteristics and/or disclosure of functional characteristics coupled with a known or disclosed correlation between function and structure. MPEP § 2163, II, 3, ii, citing *Eli Lilly* 43 USPQ2d at 1406. A "representative number of species" means that the species which are adequately described are representative of the entire genus. MPEP § 2163, II, 3, ii.

In the present application, the specification as filed discloses relevant identifying characteristics and functional characteristics of a representative number of peptides having an amino acid sequence of from about 8 to 25 amino acids having a sequence contained within amino acid residues 61-106 of SEQ ID NO: 1, which neutralize or modulate the production of anti-myelin basic protein (Claims 56-68) and/or reduce free anti-myelin basic protein (Claims 69-81). The specification further discloses that peptides of the invention can contain substitutions, deletions, or additions, as long as the peptide maintains its function of neutralizing or modulating the production of anti-myelin basic protein (anti-MBP), *e.g.*, on page 5 at lines 20-22, page 9 at lines 19-24, page 10 at lines 23-27, and page 14 at lines 22-24. Finally, given the teachings of the present invention, one of skill in the art could determine, empirically, what variation can be made to the sequence of the selected peptides with affecting the function of the peptides. (Page 9, lines 24-27). Therefore, the specification as filed provides a sufficient description of a representative number of species to demonstrate that was in possession of the invention of Claims 56-81, including substitutions, additions or deletions.

Rejection under §112, first paragraph, on the basis of amendments to SEQ ID NO: 1

Claims 56-81 also stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, it is alleged that the amendments to SEQ ID NO: 1 in the specification and in the sequence listing add new amino acids, and it is further alleged that support for the additional amino acids is not found in the specification as filed (Official Action, Secton 7, pages 5-6). Applicants traverse this rejection.

Applicants point out that the subject matter of amendments to SEQ ID NO: 1 in the specification and in the sequence listing were disclosed in the parent and grandparent applications to the present application (see discussion above). Because the sequence of human myelin basic protein (MBP) disclosed in SEQ ID NO: 1 of the Substitute Sequence Listing was known in the art at the time of filing, and is of record in the parent and grandparent applications, the inventors had possession of the claimed invention, including amino acids 1-60 and 101-170 of SEQ ID NO: 1, at the time of filing.

Rejections under 35 U.S.C. §103

Claims 56-81 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hafler *et al.* (US Patent No 5,571,500) in view of Martin *et al.* (*J Immunol.* 1990 145:540-548) or Ota *et al.* (*Nature* 1990 346:183-187). Allegedly, it would have been obvious "to substitute the fragments of MBP in the method of treating MS taught by Hafler *et al.* with the characterized immune reactive fragments of MPB taught by Martin *et al.* and Ota *et al.*" (Official Action, Secton 8, page 8). It is further alleged that one of ordinary skill in the art would have been motivated to make the substitution and would have expected success "because the peptides taught by Martin *et al.* and Ota *et al.* are know[n] to contain the immune reactivity property found in the whole MPB taught by Hafler *et al.*" and thus the claimed invention was as a whole, *prima facie* obvious (Official Action, Section 8, page 8).

Applicants traverse this rejection. Applicants submit that the Examiner has not established a *prima facie* case of obviousness by combining these references and therefore, the rejection under 35 U.S.C. § 103(a) is improper and should be withdrawn.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *See*, MPEP §§ 2142, 2143.

In the present case, there is no suggestion or motivation to modify or combine the references teachings in the manner proposed. Additionally, there is no reasonable expectation of success from the proposed combination. Because the basic criteria for a *prima facie* case of obviousness have not been met, rejection of Claims 56-81 under 35 U.S.C. §103 is improper and should be withdrawn.

No suggestion or motivation to combine references to make the claimed invention

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ 2d 1596 (Fed. Cir. 1988); *In re Jones* 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See generally, MPEP §2143, especially §2143.01. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In the present case, there is no teaching, suggestion, or motivation to combine or modify the cited references in such a way as to produce the claimed invention.

Applicants traverse the argument put forth in the Office Action that one of ordinary skill in the art would allegedly have been motivated to substitute the fragments of MBP in the method of treating MS taught by Hafler *et al.* with the characterized immune reactive fragments of MBP taught by Martin *et al.* and Ota *et al.*. In fact, the cited references provide no teaching or suggestion or motivation to combine the teachings of Hafler *et al.* with the teachings of Martin *et al.* or Ota *et al.* as proposed. Hafler *et al.* neither teach nor suggest nor provide motivation for using the immune reactive peptides such as those disclosed by Martin *et al.* and Ota *et al.* as an "autoimmune suppressive fragment" in the method of treating MS by inhalation of autoantigens

taught by Hafler *et al.* Applicants point out that Hafler *et al.* do not teach peptides of at least 8 to 25 amino acids contained within SEQ ID NO: 1, and describe an "autoimmune suppressive fragment" as "any peptide or polypeptide containing partial amino acids sequence or moieties of autoantigens and possessing the ability to suppress or prevent an autoimmune response upon aerosol administration." (Hafler *et al.*, col. 5 at lines 14-19). In contrast, Martin *et al.* allegedly teach MBP as a candidate antigen for the autoimmune process important for the pathogenesis of multiple sclerosis (MS), and but do not teach administration of MPB peptides for the treatment of MS. Ota *et al.* allegedly disclose MBP peptides and the involvement of these peptides in MS, but do not teach administration of these peptides for treatment of MS.

Not only is there no teaching or suggestion to combine reference, there is no motivation in the references to combine or modify the cited references to produce the invention of Claims 56 to 81. Here, the mere fact that the teaching of immune reactive fragments of MPB disclosed in Martin *et al.* or Ota *et al.* can be combined with the teaching of Hafler *et al.* of administering autoimmune suppressive fragments to treat MS, does not render the combination obvious. The Federal Circuit has held that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Further, the argument that a combination is "obvious to try" is not acceptable for establishing obviousness. *In re Tomlinson* 150 USPQ 623 (CCPA 1966). Finally, absent a suggestion, teaching, or motivation to combine references, such a combination is unacceptable "hindsight" that does not establish a *prima facie* case of obviousness. *In re Dembiczak* 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). Because there is no teaching, suggestion, or motivation for the proposed combination of references, this criterion for establishing a *prima facie* case of obviousness has not been satisfied and the rejection should be withdrawn.

No reasonable expectation of success

Prima facie obviousness requires a reasonable expectation of success. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d

488, 20 USPQ2d 1438 (Fed. Cir. 1991). In the present case, the combination of cited references provide no reasonable expectation of the success that has been disclosed and claimed in the present application. On the one hand, Hafler *et al.* allegedly teach administration of MBP fragments to treat MS, where any such fragment is an "autoimmune suppressive fragment." In contrast, Martin *et al.* allegedly teach MBP as a candidate antigen for the autoimmune process important for the pathogenesis of multiple sclerosis (MS), and Ota *et al.* allegedly disclose immunodominant MBP peptides and the involvement of these peptides in MS. There is no reasonable expectation that combining the method taught by Hafler *et al.* with one or more peptides taught by Martin *et al.* or Ota *et al.* would produce the claimed methods of treating MS by administering a peptide that can neutralize or modulate the production of anti-myelin basic protein (Claims 56-68) or reduce free anti-myelin basic protein (Claims 69-81). In fact, Martin *et al.* and Ota *et al.* would teach away from administering MBP peptides that are involved in MS. Because there is no reasonable expectation of success from the proposed combination of references, this criterion for establishing a *prima facie* case of obviousness has not been satisfied and the rejection should be withdrawn.

CONCLUSION

Claims 51-86 are pending in the present application and currently stand rejected. Applicants request that Claims 56-81 be reconsidered in light of the remarks presented above, and be found in condition for allowance.

A Substitute Sequence Listing is submitted herewith, disclosing the amino acid sequence of human myelin basic protein (MBP) in SEQ ID NO: 1. The specification has been amended to identify the amino acids of SEQ ID NO: 1 corresponding to the MBP peptides disclosed in the specification. The Substitute Sequence Listing and the amendments to the specification do not contain new matter and should be entered.

If the Examiner believes that a telephone interview would expedite prosecution of this application, she is encouraged to telephone the undersigned Applicants' attorney.

The Applicant believes no fee is due. However, if any fees are due in connection with this submission, please charge any such fee or credit any overpayment to Deposit Account No. 50-2212.

Respectfully submitted,

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